Case 1

Small College – First Project Falling Under the *NIH Guidelines*

Scenario:

A faculty member in the Department of Chemistry of a small liberal arts college has been awarded the institution's first NIH grant for research involving recombinant DNA (and thus its first project subject to the *NIH Guidelines*). The objective of the project is to create an effective biological solution to cleaning up oil spills. The project entails placing a gene for the production of methane monooxygenase into a plasmid, and inserting the plasmid into a marine strain of Pseudomonas (a Risk Group 1 agent). The project is limited to contained laboratory testing of the transformed bacteria's ability to break down various petroleum-based products.

The college at present has no IBC and rather than invest in the resources and staffing that would be necessary to establish one for this very limited activity, it proposes to have this activity reviewed by the IBC at a major academic medical center one mile down the road.

Questions:

1. The *NIH Guidelines* state, "Each institution conducting or sponsoring recombinant DNA research which is covered by the *NIH Guidelines* …shall establish an Institutional Biosafety Committee that meets the requirements set forth [in the *NIH Guidelines*]." Is the use of an IBC at another institution equivalent to "establishing" an IBC? Is the scenario described above thus acceptable under this provision of the *NIH Guidelines*? Should it be?

2. Could the IBC at the academic medical center adequately assess the biosafety risks posed by this activity?

3. What measures can be put in place to ensure that the investigator at the small college heeds the recommendations of the IBC at the academic medical center?

4. What conditions or characteristics would need to exist to make this situation ideal?

Modified scenario A: The project is instead being conducted in the Department of Biology. The objective of the project is to create a penicillin-resistant strain of *Streptococcus pneumoniae* - a Risk Group 2 agent and an important cause of human infections - so that the impact of combined antibiotic therapies on resistant strains can be studied in animal models.

Questions:

1. Does this scenario change any of the answers to the questions above?

2. Does the higher risk level of the organism tip the scales in favor of an IBC situated at this college? Why or why not?

3. Should the distance of the IBC matter? Would this scenario be less acceptable if the college used an IBC at an institution 100 miles away?

4. Has the modification to this scenario changed its acceptability under the *NIH Guidelines*?

Case 2

Hospital Consortium

Scenario:

A group of six research-intensive teaching hospitals located in the same city are all affiliated with a common medical school. The medical school and all six hospitals receive NIH funding for research involving recombinant DNA. Many clinical and research staff at the teaching hospitals hold faculty appointments at the medical school and collaborations between the institutions are quite common. The medical school, in fact, offers administrative support to the research activities of the hospitals, including a central IRB for the review of all human subjects protocols. IBC review, however, is presently being conducted individually by each hospital. To streamline the system further, the medical school is considering the establishment of a central IBC. The central IBC will have members from each participating institution, plus at least two local community members with no affiliation with any of these hospitals. The hospitals are conducting human gene transfer protocols involving a variety of gene delivery approaches, including plasmid, adenoviral, and AAV vectors.

Questions:

1. The *NIH Guidelines* state that each institution conducting research covered by the *NIH Guidelines* "shall establish an Institutional Biosafety Committee…" Can each hospital be considered to have "established" an IBC under this scenario?

2. The *NIH Guidelines* state, "…no research participant shall be enrolled…until...Institutional Biosafety Committee (IBC) approval (from the clinical trial site) has been obtained." Although the *NIH Guidelines* do not define "clinical trial site, " they do say, "Institutional Biosafety Committee approval must be obtained from the institution at which recombinant DNA material will be administered to human research participants" (Section IV-B-2-a-(1)). Given these provisions, is IBC approval "from the clinical trial site" possible under this scenario?

3. Can investigators at each hospital be made to heed the advice of the medical school IBC? If so, how?

4. If the biosafety review is inadequate and a problem arises, which institution should be held accountable for that situation?

5. Given the answers to Questions 1 through 4, does this scenario seem acceptable under the *NIH Guidelines*?

Modified scenario A: These hospitals are all in the same metropolitan area, but have no affiliation with a common medical school. In fact, the only formal relationship the hospitals have with one another is through a jointly managed research consortium, which solicits industry funding for clinical research, including human gene transfer trials. To facilitate the review process for industry, the consortium has established a central IRB that reviews all projects proposed for funding at any one of the six hospitals. The consortium now wishes to establish a central IBC, as well.

1. Does this scenario change any of the answers to the questions above? In other words:

    a. Can each hospital be considered to have "established" an IBC?

    b. Is IBC approval from the clinical trial site possible under this scenario?

    c. How can investigators at each hospital be made to heed the advice of the medical school IBC?

    d. What entity should be held accountable for the quality of review and oversight of any problems?

2. Given the answer provided to Questions 1a through 1d above, does this modified scenario seem acceptable under the *NIH Guidelines*?

Case 3

Investigator-Physician Collaboration

Scenario:

A researcher at a large academic medical center receiving NIH funding for recombinant DNA research is proposing a trial (funded in part by the NIH) of a gene transfer approach to renal cell cancer. The project entails the insertion of the gene for the production of interleukin-4 into patients' fibroblasts *ex vivo* using a retroviral vector. These transduced cells are mixed with patients' own cancer cells and reinjected into patients to elicit an enhanced immune response.

This procedure will be conducted at an academic medical center (AMC), but some participants in this trial are patients at a non-NIH funded oncology clinic 50 miles away. An oncologist practicing at that clinic will refer patients to the AMC, where the informed consent process and administration of the gene transfer product will occur. Under the contractual relationship between the oncologist and the principal investigator, testing to assess the initial response to the intervention will be done at the AMC, as will all future protocol-specified activities. After the intervention, patients will return home and continue to be seen by the oncologist at the clinic at regular intervals. The oncologist's participation in the research activity will be limited to providing to the investigator the results of tests conducted in the course of routine clinical care (blood, vitals) so that additional long-term clinical data can be added to the research record.

Questions:

1. Should the oncology clinic be required to have its own IBC? Why or why not?

Modified scenario A: The collaborating oncologist is at another large academic medical center that receives NIH funding for research involving recombinant DNA. This second AMC thus has its own IBC.

1. Does this change the need or rationale for having a second IBC review the protocol?

Modified scenario B: The collaborating oncologist is at a small clinic with no NIH funding, but will be conducting the initial consent process and pre-enrollment screening and testing. After the gene transfer intervention, the oncologist will conduct special protocol-specified assays. The oncologist will receive some modest compensation in exchange for his role in the project.

1. Does this change the need or rationale for having a second IBC review the protocol?

2. The *NIH Guidelines* state, "…no research participant shall be enrolled…until...Institutional Biosafety Committee (IBC) approval (from the clinical trial site) has been obtained."

    a. Should the oncology clinic be viewed as a "clinical trial site"? In answering this question, consider that the term "clinical trial site" is presently undefined in the *NIH Guidelines*, but Section IV-B-2-a-(1) does say, "Institutional Biosafety Committee approval must be obtained from the institution at which recombinant DNA material will be administered to human research participants."

    b. "Enrollment" is defined in the *NIH Guidelines* as "the process of obtaining informed consent from a potential research participant or a designated legal guardian of the participant, to undergo a test or procedure associated with the gene transfer experiment." Does the involvement of the physician at the oncology clinic constitute "enrollment" of patients? Should enrollment be taken into account in determining whether this is a clinical trial site?

Case 4

Multi-site Trial

A biotechnology company is undertaking testing of a gene transfer product for a Phase 1 IND. This is a privately funded trial, but the company does get NIH funding for another activity involving recombinant DNA. As a condition of continuing to receive that NIH funding, all of its research involving recombinant DNA must comply with the *NIH Guidelines*, including this trial.

The testing for this trial will take place in the offices of four physician practices located in Seattle, Los Angeles, Baltimore, and Dallas. Each site will enroll about five patients each. The product is a tumor antigen that will be expressed by plasmid DNA (an agent not infectious to humans) injected intratumorally into patients with melanoma.

As part of its compliance with the *NIH Guidelines*, the company is arranging to have the protocol reviewed by an IBC. However, each of the sites is a small, non-NIH funded physician practice without the infrastructure or means to establish its own IBC. So the company has proposed the use of a commercial IBC.

The commercial firm will create an IBC for each of the four sites. Each IBC is composed of five members. The IBCs of all four sites will share three members, who are experts in biosafety and the science in question. These expert members are located in research universities in Boston, San Francisco, and Minneapolis. In addition to these shared, geographically distant experts, each IBC will include two local members who work within 25 miles of the site. One of these individuals has expertise in environmental health and biosafety; the other is a non-scientific lay person.

The two local members will conduct site visits at the physicians' offices, assess the ability of the staff to appropriately handle the recombinant material, and evaluate decontamination and disposal practices.

Each IBC will then be convened by conference call to conduct its review of the protocol in question, taking the findings from the local site visit into account.

Questions:

1. The *NIH Guidelines* state, "…no research participant shall be enrolled…until...Institutional Biosafety Committee (IBC) approval (from the clinical trial site) has been obtained." Is approval from the clinical trial site possible under this arrangement?

2. How can the investigators at each site be made to heed the recommendations of the site's IBC?

3. What entities (site, sponsor, both?) should be responsible for how each IBC functions? How can such accountability be created?

4. Section IV-B-2-b of the *NIH Guidelines* make IBCs responsible for conducting an "(i) independent assessment of the containment levels required by the *NIH Guidelines* for the proposed research; (ii) assessment of the facilities, procedures, practices, and training and expertise of personnel involved in recombinant DNA research; [and] (iii) ensuring that all aspects of Appendix M have been appropriately addressed by the Principal Investigator." Could this type of IBC adequately address those matters?

5. Furthermore, IBCs are responsible for ensuring that no research participant is enrolled in a human gene transfer experiment until the RAC review process has been completed, and for ensuring compliance with all surveillance, data reporting, and adverse event reporting requirements set forth in the *NIH Guidelines*. Could this sort of IBC reasonably accomplish that?

6. Section IV-B-2-a of the *NIH Guidelines* details membership requirements for IBCs, and provides for a minimum of two community members. The *NIH Guidelines* do not specify how many IBC members must be employees of the institution. Should they?

Modified scenario A: The product is a VEGF gene sequence delivered by replication incompetent adenovirus to heart tissue through intravenous injection to promote the growth of lateral vasculature.

Questions:

1. Should these IBCs have a role in the ongoing surveillance of the risks associated with this kind of protocol? If so, could these IBCs serve that role? If not, how could such safety surveillance be accomplished?

Modified scenario B: The product is a replication deficient lentivirus carrying an antisense sequence targeted to HIV in the treatment of HIV infection.

Questions:

1. Does this scenario change anything about your view of Question 1 under Modified scenario A?

Modified scenario C: The commercial IBC includes a sixth member who is a clinical study nurse and an employee of the site.

Questions:

1. Does this scenario change anything about your view of Question 1 under Modified scenarios A or B?

Modified scenario D: The company receives no NIH funding whatsoever, and is thus not obliged to follow the *NIH Guidelines*. Nonetheless, it wishes to submit its protocols voluntarily, as is encouraged under the *NIH Guidelines*.

Questions:

1. Should its IBCs then be held to the same standards and requirements as if it were a mandatory compliance situation?

2. Should OBA accept protocols that do not fully comply with the IBC or other requirements set forth for mandatory submissions?